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Associations between migraine, celiac disease, non-celiac gluten sensitivity and activity of diamine oxidase

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ABSTRACT

Background and pilot study: Recent reports reveal a close relationship between migraine and gastrointestinal disorders (GI), such as celiac disease (CD) and non-celiac gluten sensitivity (NCGS). CD is a genetic autoimmune disorder, which affects the mucosa of the small intestine. Gluten, found in various grains, not only plays a major role in the pathophysiology of CD and NCGS, but also aggravates migraine attacks. Another common food component, which can induce migraine headaches, is histamine. Diamine oxidase (DAO) is an enzyme, which degrades histamine. Reduced activity of DAO means reduced histamine degradation, which can cause histamine build-up and lead to various symptoms, including headaches and migraine. In this paper we propose a hypothesis, that in pathogenesis of migraine, low serum DAO activity is related to CD and NCGS. We also conducted our own pilot study of 44 patients with severe migraine in efforts to evaluate the co-presence of decreased serum DAO activity and celiac disease/NCGS in patients. 44 consecutive migraine patients were divided into 2 groups: decreased DAO activity (group 1; n = 26) and normal DAO activity (group 2; n = 18). All patients were screened for celiac disease. The diagnosis of NCGS was made after exclusion of CD, food allergies and other GI disorders in the presence of gluten sensitivity symptoms. Furthermore, dietary recommendations were given to all participants and their effects were assessed 3 months after the initial evaluation via the MIDAS (Migraine Disability Assessment) questionnaire.

Results and conclusions: Only 1 patient fit the criteria for celiac disease, rendering this result inconclusive. Pathological findings of the remainder of patients were attributed to NCGS (n = 10). 9 of 10 patients with NCGS belonged to the decreased serum DAO activity group (group 1; n = 26), suggesting a strong relationship between reduced serum DAO activity and NCGS. MIDAS questionnaire revealed, that patients with decreased serum DAO activity were more severely impacted by migraine than those with normal DAO activity, and this remained so after our interventions. Dietary adjustments significantly reduced the impact of migraine on patients' daily activities after 3 months in both groups. We argue, that migraine, celiac disease and NCGS may benefit from treatment with a multidisciplinary approach, involving neurologists, gastroenterologists and dietitians.

Introduction

Migraine is a common headache disorder with prevalence of approximately 12% of total population [1]. It can have a severe impact on the quality of life of an individual by affecting personal life, social life and work performance, while the treatment costs create a considerable economical burden for the healthcare system [2].

Recent reports reveal a close relationship between migraine and gastrointestinal (GI) disorders [3]. It is becoming evident that proper treatment of underlying GI conditions, such as celiac disease, reduces the severity and frequency of migraine headaches [4]. Celiac disease is a genetic autoimmune disorder, which affects the mucosa of the small intestine [5]. Gliadin, a component of gluten, is key to eliciting a damaging immune response, hence observed morphological changes can be controlled via a gluten-free diet [6]. Diagnosis of CD requires serological, histological and genetic confirmation [5]. If patients do not meet the diagnostic criteria of CD, but experience gluten sensitivity, non-celiac gluten sensitivity (NCGS) can be diagnosed, provided food allergies, CD and other GI diseases are ruled out [7].

Diamine oxidase (DAO) is an enzyme, which degrades histamine. Reduced concentrations or activity of DAO can lead to elevation in histamine concentration, leading to allergic reactions, headaches and

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migraine [8–13]. Furthermore, histamine intolerance has been shown to closely resemble responses elicited by gluten, which indicates, that a close relationship between histamine and gluten may be present [14].

The hypothesis

Our hypothesis is that migraine, alongside decreased serum DAO concentration and sensitivity to histamine, is closely related to gluten sensitivity (celiac disease and NCGS). The hypothesis stems from epidemiological and pathophysiological evidence, presented below.

Supporting evidence

Central and enteric nervous systems

Common pathophysiological ground for gastrointestinal and neurological diseases can be established by appreciating the relationship between the enteric nervous system (ENS) and central nervous system (CNS). The brain-gut axis idea has been proposed, suggesting that information is relayed and integrated both from the CNS to ENS, and from ENS to CNS [15]. As a result, the possible connections between GI syndromes and neurological syndromes can be explored and would suggest that CNS-ENS interaction may be pathophysiologically significant for co-occurrence of diseases, such as migraine and celiac disease [16].

Migraine, celiac disease and NCGS

A number of epidemiological studies have found a close relationship between migraine and gastrointestinal disorders, such as celiac disease and NCGS. A case-control study of 502 patients with celiac disease and NCGS demonstrates a bigger prevalence of migraine compared to the general population [17], while another case-control study of 90 migraine patients reveals a reverse association, showing increased celiac disease prevalence in patients with migraine compared to the general population [18].

Such associations are grounded in a growing body of evidence, which suggests that the diseases have extensive pathophysiological links. On a molecular level, it has been implied that toxic gluten peptides, which induce a damaging immune response to the small intestine in celiac disease, are a product of an extracellular enzyme transglutaminase 2 (TG2) [19]. Increased TG2 expression results in more toxic gluten peptides, eliciting a more severe immune response. TG2 expression is upregulated by tumor necrosis factor alpha (TNFa) through p38 MAPK (mitogen-activated protein kinase) pathway [20]. However, activation of MAPK pathways not only increases TG2 expression, but also upregulates calcitonin gene-related peptide (CGRP) synthesis and release [21], which has been closely associated with migraine [22]. Therefore, celiac disease can be presumed to be associated with migraine on a molecular level.

Migraine and gluten

Gluten has been demonstrated to have damaging effects on the nervous tissue in patients with celiac disease and NCGS. The effects can range from cerebellar ataxia to depression and migraine [23]. More importantly, such syndromes can occur in well-nourished patients, excluding malnutrition as an aetiological factor. In a prospective study of 215 patients with axonal neuropathy, 34% had positive IgA antigliadin antibodies, compared to 12% in the healthy control group, revealing increased risk of both gluten sensitivity and celiac disease in patients with peripheral neuropathy, compared to the general population [24]. In order to analyze the actual effects on gluten itself, a number of studies prescribed gluten-free diets to patients with migraine, which had statistically positive results on the frequency and severity of migraine attacks [4,18].

Migraine, serum DAO activity and histamine

Histamine is a biogenic amine, which can initiate and aggravate migraine attacks [25]. It is present in many foods, and some migraineurs tend to avoid foods high in histamine, such as certain fish, cheeses, processed meat, fermented foods and alcoholic beverages, presumably due to them provoking migraine attacks [26]. Histamine is metabolised to inactive components by diamine oxidase (DAO). DAO is released into GI tract lymphatically, which is a response to increased histamine release. It has been hypothesized that secretion of DAO has a purpose to control the unwanted effects of histamine [27]. Therefore, it is rational to presume, that decreased DAO activity would imply hindered ability to degrade histamine and greater subsequent unwanted effects of histamine release. Izquierdo-Casas et al. (2018) found that decreased serum DAO activity was more closely associated with migraine headaches rather than non-migraine headaches [28], and their subsequently conducted randomized controlled trial of 100 patients with migraine and decreased DAO activity (2019) have found, that administering DAO supplements in these patients significantly reduced the duration of migraine attacks by 1.4 h ($p = 0{,}0217$), while the placebo group did not experience significant change (0,9 h) [29]. Furthermore, García-Martín et al. (2015) discovered certain genes, responsible for decreased DAO activity, and that patients with such genes were significantly more likely to develop migraine [12].

Migraine, DAO activity and celiac disease/non-celiac gluten sensitivity – our findings

The information regarding the link between serum DAO activity and mentioned gastrointestinal disorders is scarce. To address the issue we conducted our own pilot study in efforts to evaluate the co-presence of decreased serum DAO activity and celiac disease/NCGS in patients with severe migraine. Furthermore, we gave general dietary recommendations regarding gluten sensitivity to all participants and assessed its effects 3 months after the initial evaluation.

Pilot study

Objectives

1. To evaluate the correlation between decreased DAO activity and the prevalence of celiac disease and NCGS in patients with severe migraine.
2. To evaluate the impact of migraine on patients' daily activities before investigation and 3 months post-investigation.

Methods

59 consecutive patients with severe migraine, treated in Hospital of Lithuanian University of Health Sciences Kauno klinikos from December 2015 to December 2016, presenting with symptoms related to celiac disease or non-celiac gluten sensitivity (NCGS) were considered in the study. Afterwards, 15 patients were excluded (other cause of dyspepsia identified – 2 patients; lifestyle considered to be too hectic to follow administered treatment – 2 patients; patients not following administered migraine treatment with previously diagnosed migraine – 4 patients; consent not given – 7 patients). As a result, 44 patients (5 male, 39 female, aged 18+, mean age 41,31 ± 95% CI 37,93–44,70) were enrolled in the study. Severe migraine was defined as experiencing 4 or more migraine attacks in a month and/or having drug-resistant migraine. Diamine oxidase (DAO) activity in serum was tested for all patients. Patients were divided into 2 groups: decreased DAO activity (group 1; $n = 26$) and normal DAO activity (group 2; $n = 18$). Prevalence of celiac disease and NCGS were evaluated with tissue transglutaminase antibody titer in serum (anti-tTG) and histological examination of duodenum mucosa. Anti-tTG was tested by ELISA

Table 1
Comparison of anti-tTG titers between groups 1 and 2.

Characteristics	Group 1, n (%) (Decreased DAO activity)	Group 2, n (%) (Normal DAO activity)	p
Participant count	*n = 26*	*n = 18*	χ^2 = 2,23; df = 1; p = 0,14
anti–tTg–IgA concentration:	–	–	
Normal value (< 12 U/ml)	23 (88,46)	18 (100,00)	
Positive findings (> 18 U/ml)	3 (11,54)	0 (00,00)	

and histologic samples were obtained by endoscopic biopsy. Histologic findings were interpreted in accordance with the Marsh classification. The impact of migraine on daily activities was evaluated using Migraine Disability Assessment (MIDAS) on first admission and again in 3 months, after the patients had received dietary recommendations. All data were stored using Excel 2007, and statistical significance of results was tested with SPSS 2.0. Descriptive statistics methods were used to calculate average age and other mean values. Chi-square test and Fisher's exact test were used for categorical variables (Chi-square was used for larger samples, whereas Fisher's exact test was used when samples are small), whereas *t*-test was used to evaluate power for continuous variables; $p < 0,05$ was held significant in all tests.

Results

1. Association of DAO activity with celiac disease and NCGS.

Anti-tTG findings

In group 1, 3 of 26 patients had positive findings (18 U/ml), whereas in group 2 no patients had abnormal results (χ^2 = 2,23; df = 1; p = 0,14). Results are presented in Table 1.

Histologic findings

In group 1, 8 of 26 patients displayed abnormal duodenum mucosa (7 – Marsh I; 1 – Marsh IIIA), whereas in group 2 only 1 patient (Marsh IIIA). Results are presented in Table 2.

Combined data

According to clinical, laboratory and histologic findings, only 1 patient fit the criteria for celiac disease. The pathological findings of the remainder of patients were attributed to NCGS. NCGS prevalence in both groups are presented in Table 3.

2. Evaluation of impact of migraine on patients' daily activities before investigation and 3 months post-investigation.

The evaluation was carried out via the MIDAS questionnaire. The first evaluation occurred during the first consult with a neurologist. The second evaluation took place after 3 months, after the patient had already had a consult with a gastroenterologist and had been informed about general dietary recommendations regarding gluten sensitivity and histamine intolerance. Testing was made for both groups 1 and 2.

Patients in group 1 (decreased DAO activity) showed statistically lower average of days, during which patients' daily activities were impaired (Total: 85,54 CI [61,54–109,54] on first admission, and 71,04 CI [49,70–92,37] after 3 months, a decrease of 14,50, p = 0,05), as well as slightly decreased pain severity during headaches (7,50 CI [7,03–7,97] on first admission, and 7,15 CI [6,75–7,56] after 3 months, a decrease of 0,34, p = 0,004).

Table 3
Comparison of prevalence of NCGS between groups 1 and 2.

Characteristics	Group 1, n (%) (Decreased DAO activity)	Group 2, n (%) (Normal DAO activity)	p
Participant count	*n = 26*	*n = 18*	χ^2 = 5,43;
Prevalence:	–	–	df = 1; p = 0,02
Disease-free	16 (61,54)	17 (94,44)	
Non-celiac gluten sensitivity	9 (34,62)	1 (5,55)	

Patients in group 2 (normal DAO activity) also experienced statistically lower average of days, during which patients' daily activities were impaired (Total: 48,06 CI [38,89–57,22] on first admission, and 38,89 CI [31,64–46,14] after 3 months, a decrease of 9,17 days on average, p = 0,003), as well as slightly decreased pain severity during headaches (7,11 CI [6,70–7,52] on first admission, and 6,61 CI [6,12–7,10] after 3 months, a decrease of 0,50, p = 0,02).

When comparing the average number of days with migraine headache in both groups prior to our interventions, *t*-test reveals, that the group 1 (decreased DAO activity) is much more affected than group 2 (85,54 days vs. 48,06 days, respectively, p = 0,0001). This remains true after 3 months (71,04 days vs. 38,89 days, respectively, p = 0,0001).

Discussion

In our study, only 1 migraine patient fully fit the criteria for the diagnosis of celiac disease, therefore, no clear statements can be made about the difference in the prevalence of celiac disease between patients with different DAO activity. A shortage of the total number of enrolled participants may have led to this result.

However, 9 out of 10 migraine patients diagnosed with NCGS were found to have decreased DAO activity, suggesting a positive association between migraine, NCGS and serum DAO activity and supporting our hypothesis. The causal relationship and the nature of the associations remain unclear and many models of explanation may fit. From a clinical perspective, the current results suggest, that in patients with gluten sensitivity (provided CD, food allergies and other GI diseases are ruled out), it would be rational to test serum DAO activity and consider addressing migraine treatment through dietary changes, such as reducing gluten and histamine content in foods. Therefore, gluten sensitivity and response to diet in migraine patients may prove to be a useful screening

Table 2
Comparison of duodenum histological findings between groups 1 and 2.

Characteristics	Group 1, n (%) (Decreased DAO activity)	Group 2, n (%) (Normal DAO activity)	p
Participant count	*n = 26*	*n = 18*	χ^2 = 5,76; df = 2; p = 0,06
Histology, in accordance with Marsh:	–	–	
Normal duodenum mucosa	18 (69,23)	17 (94,44)	
Marsh I	7 (26,92)	0 (00,00)	
Marsh IIIA	1 (3,85)	1 (5,56)	

tool.

The evaluation of impact of migraine on patients' daily activities before investigation and 3 months post-investigation revealed, that the quality of life in migraine patients, who have decreased serum DAO activity, is more severely impacted than in those with normal DAO activity, and this remains true after treatment. Therefore it seems, that DAO activity is related to migraine severity. Luckily, results demonstrated a noteworthy reduction in the number of days, during which patients' daily activities were impaired; as well as slightly decreased pain severity during headaches in both groups. The changes were likely to be caused by patients' dietary adjustments due to the second evaluation taking place after the patients had already had a consult with a gastroenterologist and dietitian and had been informed about the dietary recommendations regarding gluten sensitivity and histamine intolerance. These results support the hypothesis, that migraine, gluten sensitivity, and reduced serum DAO activity are related and also suggest, that in patients with gluten sensitivity and reduced DAO activity, diet can be a major treatment factor.

Since migraine and GI disorders have been found to be closely related [3], we recommend to treat migraine, celiac disease, and NCGS with a multidisciplinary approach, involving neurologists, gastroenterologists and dietitians. We hope this information will help to improve the treatment of severe migraine, gastrointestinal disorders, and the pain that accompanies these disorders. Earlier and more accurate identification of comorbid conditions can reduce the frequency of migraine headaches, reduce treatment costs, and improve the quality of patients' lives.

Although our pilot study supports the hypothesis, it does not prove it by far. The study itself is limited by a wide array of factors, such as inferior study design and small sample size, which do not allow to draw decisive conclusions. Furthermore, although the data about patients' comorbid conditions and previously used medications were obtained at the time, information was not documented. Also, even though we gave patients general recommendations regarding histamine and gluten containing products, strict and consistent control over their diet was not maintained, therefore, it cannot be concluded, that diet was the main factor in observed improvements. All of the mentioned limitations may create bias and subsequently, inaccurate results, therefore, further research on the topic is warranted.

Conflict of interest

Authors disclose, that there are no financial or personal relationships with other people or organisations that could inappropriately influence their work.

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